INTRODUCTION

Aging is characterized by loss of physiological function and increasing susceptibility to disease. A prominent theory of the cause of aging has been the free radical theory, which posits that the accumulation of molecular damage from free radicals (or radical oxygen species, ROS) causes aging. The free radical theory has been called into question, as it's been found that many treatments that extend life in experimental animals require ROS, and that antioxidants may blunt life extension. Another theory of aging holds that aging is a "quasi-program", the necessary consequence of the growth program. Prominent in this theory are the roles of the mammalian target of rapamycin (mTOR) and insulin receptor signaling, both of which are necessary for growth. Inhibiting insulin signaling as well as mTOR leads to longer lifespan in many experimental animals.

One of the most consistent extenders of lifespan and inhibitors of aging is calorie restriction (CR), in which calories are restricted by 30% or more. Animals subject to CR not only live longer, but show a robust physiological response, including upregulated antioxidant enzymes such as glutathione peroxidase and superoxide dismutase. This raises the question of the reason, if any, in evolutionary terms, for this response. Is this response something that just happens when the growth mechanisms, such as mTOR, are throttled back? The quasi-program theory of aging predicts this.

Life history theory, however, predicts that organisms respond physiologically to important changes in their environments, such as temperature, frequency of predators, and food supply. They do this to maximize their fitness in evolutionary terms. Therefore, life history theory predicts that the response to CR is purposeful, a means by which the organism survives adverse conditions in order to survive and reproduce another day, when conditions again become favorable.

It can be seen that the quasi-program theory of aging may be at odds with life history theory. One or the other may need adjusting.

LIFE HISTORY THEORY AND CALORIE RESTRICTION

Life history theory attempts to understand how organisms allocate their limited resources among
growth, reproduction, mating effort, and parental investment.1 These allocations are determined by natural selection so as to provide for the greatest inclusive fitness, including the largest number of viable offspring, given the conditions in which the organism lives. Organisms also change their resource allocations according to environmental signals, such as presence or absence of food and predators, or temperature differences.

Life history theory has postulated that organisms exist along a spectrum that is either r-selected or K-selected. In the former, organisms are oriented towards producing large numbers of offspring with little parental investment; fish, for example, are archetypes of r-selection, producing vast numbers of fertile eggs, yet parental investment in offspring after egg-laying is zero. In K-selection, organisms produce fewer offspring but with larger parental investment; the offspring may take a relatively long time to mature, and males (fathers) may play a role in raising them. Humans are perhaps the archetype of K-selection.

The theory predicts that certain environmental conditions will cause the organism to shift its strategies for growth and reproduction. For example, abundant food or its opposite, famine conditions, may do this, reproduction being postponed when little food is available. It’s been shown that human females attain menarche at an earlier age when a stepfather lives in the household; age of menarche is also related to the degree of polygyny in a society.2 Thus humans (and other organisms) adjust their life history strategy to attempt to attain the most advantageous reproductive outcome.

Calorie restriction (CR), and CR mimetics, such as resveratrol and metformin, extend lifespan. The means through which CR and its mimetics do this have been much researched and debated. It does not appear to be the case that CR extends lifespan through limitation of damage by reactive oxygen species, since in many cases antioxidants negate the effects of CR mimetics; the opposite appears to be the case, namely that reactive oxygen species are required for lifespan extension.3 Metformin has been shown to increase the production of reactive oxygen species as at least one mechanism of action.4

The question arises whether an organism’s response to CR is a purposeful response, or whether it is merely something that happens when not enough food is available. Life history theory would predict that the response is purposeful, since fewer nutrients ingested signals a significant environmental deterioration, and the organism may well need to adjust its life history strategy in response. For example, it would make sense to postpone reproduction in the face of less food, since parent or offspring may not be well-nourished, with both having diminished odds of survival. Indeed, reduction of fertility is one response to CR.

However, the notion that the response to CR on the part of an organism is deliberate or purposeful gives rise to a number of paradoxes, which have been well-described by Blagosklonny.5 In the case of declining fertility in the face of CR, the allocation resource paradox would seem the most relevant. Allocating resources to anti-aging repair in the face of famine conditions is likened to moving into a new, luxury apartment in the face of losing one’s job. It seems paradoxical for an organism to allocate resources to a process, anti-aging repair, that it can do wholly without in the face of abundant nutritive resources. Blagosklonny states explicitly, “CR extends lifespan not for any purpose, not in order to live longer. Simply, TOR, which is stimulated by nutrients, drives both growth and aging.”5

Theories of the causes of aging are many. One hypothesis, that elucidated by Blagosklonny, posits that aging is a “quasi-program”, a latent development of the growth program.6 This can account for the effects of CR on aging, since it is the effect of CR and its mimetics on mTOR and other growth pathways, notably the insulin/IGF-1 pathway, that accounts for their lifespan-extending effect. CR, by causing a halt to the growth program, also calls a halt to the quasi-program of aging. Blagosklonny asserts that this hypothesis can account for the various paradoxes of aging, including that of the allocation of resources. The resolution to this paradox lies in the fact that no resources are actually allocated, so the idea that this occurs during times when resources are in short supply becomes moot; all that actually happens is that growth ceases, and with it, aging.
Other theories of the causes of aging, such as that of accumulation of molecular damage by reactive oxygen species, do not seem to be able to resolve the many paradoxes of aging. For example, the lifespan-extending effects of hormesis seem to work by causing damage, with the subsequent upgrading of stress-response mechanisms. So here we have a case where damage supposedly both helps and harms an organism.

As has been stated above, life history theory predicts that organisms will adjust their life history in response to environmental signals, such as lack of food. Now, the adjustments in life history that an organism makes must have a biological basis. For example, earlier puberty is caused by variations in amount and timing of hormones. In this particular case, growth (maturity) has accelerated in order to promote a more optimal life history, i.e. greater inclusive fitness, including greater numbers of viable offspring. The acceleration of growth will presumably, if the quasi-program theory of aging is correct, also mean accelerated aging.

But what would be the proximal biological mechanism through which an organism adjusts its life history program in the face of lack of food? In fact, the response to CR looks like just such a mechanism. The cessation of fertility while food is restricted, for example, bears the mark of an adjustment to life history. Similarly, a decrease in IGF-1, a growth factor, means that the organism will cease growth during food shortage, which is what life history theory would predict. Calorie-restricted humans have reported a drop in sex drive, and CR does in fact result in lower levels of sex hormones. Again, life history theory would predict this. These are examples of phenotypic plasticity, which life history makes use of to adjust strategies among growth, reproduction, and mating effort.

Watve and Yajnik have suggested that growth, as manifested in insulin resistance (IR), may be a physiological mechanism that causes a switch to a more K-selected life history. In this theory, gestational insulin resistance causes a greater investment in offspring, since the placenta is relatively less dependent on insulin than other tissues; IR also has a negative effect on ovulation, so fewer offspring will be produced. They also show that IR could be of advantage in younger people, with more nutrients going to the brain, and that actual pathology may only be important at older ages, when natural selection is weaker.

This gives rise to another paradox. The organismal response to CR, whether or not it is indeed deliberate and purposeful, resembles a shift to a more K-selected life history, with fewer offspring, less mating effort, and longer life. But IR, as we saw above, has also been postulated to cause a switch to K-selection. The paradox here is that both more and less food would cause a switch to K-selection. However, if IR is mere pathology, and not a life history switching mechanism, then no paradox arises.

However, IR also accelerates aging. It could even be said that metabolic diseases such as diabetes are archetypes of aging, with high levels of oxidative stress, inflammation, and mitochondrial dysfunction, which are all characteristic of aging. But K-selection involves greater parental investment in offspring, which also implies longer life. Between species, more K-selected organisms live longer than r-selected. In humans, short people, i.e those who experience less growth, live longer. Lower levels of growth hormone are associated with less cancer, which is a disease associated with aging. So it seems doubtful that IR is anything more than mere pathology, or at least, that its main purpose is to act as a life history switch.

The main paradox that arises here is whether the response of organisms to CR is a deliberate, purposeful one or not. Since life history theory, a main component of the theory of evolution, predicts that organisms will respond to various features of their environment with a change in life history, and since lack of food is a crucial environmental component impinging on survival and reproduction, we would expect that the physiological response to CR is part of the process of a change in life history strategy. On the other hand, if the organismal response to CR is not deliberate or purposeful, but merely what happens when the developmental program of growth is throttled back, then life history theory may need adjustment. For it seems that responding to a lack of food in the environment would be a main function of strategy in life history. An organism must alter its life history when the
environment changes in such a crucial way.

Evidence that may resolve the conundrum between life history theory and CR is that coming from studies of intermittent fasting (IF). Most studies of IF have shown that it results in most of the same beneficial effects against aging as does CR, even when experimental animals or humans ingest the same amount of calories as ad lib fed animals or humans. It seems doubtful that deliberate, purposeful changes in physiology accompanied by a switch in life history would come about as a result of the absence of food for a few hours up to one day, since such absences must have commonly occurred during the course of evolution, at least in larger animals. (As well as some individual animals, which might be unable to hunt or forage due to an injury, or bad weather, for example.)

Yet IF also presents us with the notion that halting the growth program of mTOR and related systems periodically for a mere few hours at a time also calls a halt to aging. On theoretical grounds, growth and development, on the one hand, and aging, on the other, would have to be intimately linked indeed.

Moreover, the physiological changes that occur in CR and IF result in organisms that appear much younger than ad lib fed animals, even when CR or IF are initiated relatively late in an animal's life. This looks not like a mere halt in the quasi-program of aging, but its reversal, which would lend some evidence to it being a purposeful change in life history.

**BIBLIOGRAPHY**


